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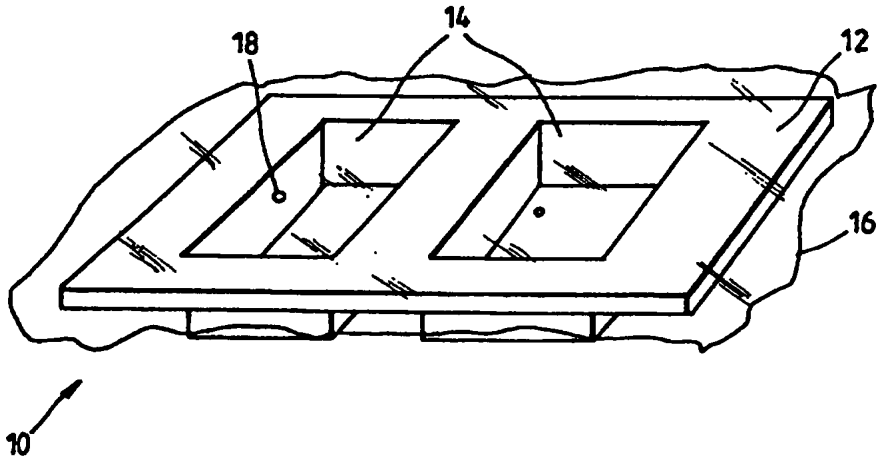

(57) Abstract

The invention is directed to a method of drying a material comprising providing a container (10, 40) which comprises an impermeable membrane (16, 42), placing the material into said container, closing the container, and drying the material in the container, wherein the closed container has one or more holes (18, 44) pierced therethrough, and wherein said hole or holes is/are sufficiently enlarged to allow water vapour or solvent to escape but sufficiently small to ensure that material is kept within the container. Also disclosed is a container adapted for use in the method of drying, wherein the container (10, 40) comprises an impermeable membrane (16, 42) having one or more holes (18, 44) pierced therethrough, the hole or holes being sufficiently large to allow water vapour or solvent to escape but sufficiently small to ensure that the material is kept within the container. The invention is particularly suited for the production of nasal inserts or "bougies".

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METHOD FOR DRYING A MATERIAL IN A CONTAINER HAVING ONE OR MORE PIERCED HOLES

The present invention relates to a new method of drying and to dried formulations.

Freeze-drying or lyophilization is a widely used method for the stabilization of otherwise easily degraded substances. It is used in the preservation of micro-organisms, food items, biological products and pharmaceuticals.

In a conventional freeze-drying method, a glass vial is partially filled with a solution of the substance to be freeze-dried and placed in a freeze-dryer. The vial is only partially stoppered and remains open throughout the freeze drying process to allow water vapour to escape from the frozen solution. Typically, a "plug" of dry material is left at the bottom of the vial, once freeze-drying is complete.

In certain pharmaceutical applications, it is often desirable to produce the freeze-dried product in a packaged form, ready for administration. It may be desirable, for example, to produce freeze-dried pharmaceutical tablets for oral administration. WO-A-9412142 discloses a method of freeze-drying in which liquid dosages are introduced into the depressions of a blister film. Following freeze drying, a plastics sheet is placed over the depressions and the blisters are sealed.

Freeze-dried materials however are usually fragile, and freeze dried "plugs" have a tendency to disintegrate into pieces and fine powder. Thus, freeze-dried residues in

an open blister film are easily ejected by static charges, air currents or by handling operations prior to film sealing.

The active agents of certain drug formulations are often unsuitable for oral delivery as they are broken down by the digestive activity of the gut. Such active agents include, for example, DNA and peptides which might be best absorbed across the buccal and/or nasal mucosae. Conventional freeze-drying, however, generally produces powder formulations which have very low bulk density, poor flow characteristics and which are difficult to administer reproducibly, for example, to the nasal and buccal mucosae. Thus, it may also be desirable to produce freeze-dried pharmaceuticals which expedite delivery to such mucosal surfaces.

Conventional freeze-dried drug formulations also tend to disperse easily and very rapidly in aqueous solution. Applied to a mucosal surface, such as an oral, oesophageal or nasal surface, such formulations have low residence characteristics which may impair the rate and efficiency of active agent uptake.

Nasal administration of pharmaceuticals using nasal inserts or "bougies" is seen as a route for systemic or local pharmaceutical delivery and as a possible alternative to intravenous administration. Such a route of administration may be especially suited for the delivery of nucleic acids, peptides, proteins and low dose drugs such as nicotine. However such nasal inserts as well as

displaying good pharmaceutical stability should desirably have a certain degree of mechanical strength to allow insertion into the nose, become bioadhesive and rapidly hydrate once in the nose.

The realisation of this has hitherto been slow and this may be due in part to not being able to fulfill or address some of the abovementioned desirable properties.

It is among the objects of the present invention to obviate or mitigate at least one of the aforementioned disadvantages.

According to a first aspect of the present invention, there is provided a method of drying a material comprising the steps of:

a) providing a container which comprises an impermeable membrane,

b) placing the material into said container,

c) closing the container, and

d) drying the material in the container, wherein the closed container has one or more holes pierced therethrough, and wherein said hole or holes is/are sufficiently large to allow water vapour or solvent to escape but sufficiently small to ensure that the material is kept within the container.

Preferably, the material is dried by freeze-drying. Alternatively, the material is dried by solvent evaporation, for example using a vacuum.

According to a second aspect of the present invention, there is provided a method of freeze-drying a material comprising the steps of:

a) providing a container which comprises an impermeable membrane,

b) placing the material to be freeze-dried into said container,

c) sealing the container, and

d) freeze-drying the material in the container, wherein the closed container has one or more holes pierced therethrough, and wherein said hole or holes is/are sufficiently large to allow water vapour or solvent to escape but sufficiently small to ensure that the material is kept within the container.

Preferably, the method further comprises the step of overpackaging the container with the material to be dried. Most preferably, the container is sealed in a second impermeable container to prevent water vapour from diffusing into the first container through the holes once drying is completed.

Alternatively or additionally, each hole may be resealed, for example, with an adhesive or welded patch.

The material to be dried may be introduced into the container either before or after holes are made in the impermeable membrane. In one embodiment, the material to be dried is injected into the container by means of a filling needle so that a hole is made in the impermeable membrane at the time of filling.

The material to be dried may initially be in solution, ie. the material may be dissolved in a solvent such as water. Alternatively, the material may be in the form of a wet slurry as described for example in US5,145,684, wherein the material is dispersed within a liquid carrier.

According to a further aspect of the present invention, there is provided a container adapted for use in a method of drying, wherein the container comprises an impermeable membrane having one or more holes pierced therethrough, the hole or holes being sufficiently large to allow water vapour or solvent to escape but sufficiently small to ensure that the material is kept within the container.

The container may comprise a blister film having a plurality of regularly spaced depressions. An impermeable membrane is placed over the blister film and sealed thereon. The impermeable membrane may be placed over the blister film either before or after the material to be dried is introduced into the blister film. In the former case, the material may be introduced into the blister film through a hole in the impermeable membrane or by a filling needle(s) which makes the hole(s). The membrane is preferably formed of a plastics material or a laminate of for example, aluminium and a plastics material.

In one embodiment, the blister film may be in the form of a tray comprising a plurality of preformed semi-cylindrical cavities. The impermeable membrane may comprise preformed holes which are regularly spaced such

that in use at least one hole is positioned over a cavity when the membrane is placed in contact with the tray. The impermeable membrane may be provided from a roll. In this manner the preparation of the container(s) is suitable in a semi- or fully automated process.

Alternatively, the container may be composed entirely of an impermeable membrane. The membrane may be in the form of a tube and sealed at both ends. Alternatively, the container may take the form of a sealed bag or pouch. Additionally the container may be tubular in form each end thereof being covered by the membrane. Such a construction is designed to allow easy removal of the lyophilised material from the tube.

The impermeable membrane may be pierced with one or more holes, or the hole(s) may already be present in the membrane material. In certain embodiments, the membrane may be preformed with holes which are uniformly spaced. The holes are large enough to allow water vapour or solvent to escape during the drying step. They are sufficiently small however to ensure that the material remains within the confines of the container before, during and after drying. The holes are substantially circular in cross-section and have a minimal tortuosity. Preferably, the overall area covered by the hole or holes is large enough for water vapour or solvent to escape during the drying stage at a rate which is more than 40% the rate at which water vapour or solvent is lost from an open container. Typically, the rate of water vapour or solvent loss is more than 70% of

the rate of loss from an open container. In a particular embodiment of the present invention, the area covered by the holes allows water vapour or solvent to be lost at substantially the same rate as from an open container. It has been found surprisingly that an extremely small area covered by the holes allows water vapour or solvent to be lost at substantially the same rate as from an open container. Typically the total area covered by the holes may be less than 1% or even 0.5% as compared to the open area of an open container.

Hole sizes may vary from 10 microns to 2 mm across. Preferably, each hole has a diameter of between 100 to 1000 microns; typically, between 250 and 800 microns and in a preferred embodiment, the hole has a diameter of 550 microns.

In a further aspect there is provided a closed container comprising a dried material, wherein the container comprises an impermeable membrane having one or more holes pierced therethrough the hole or holes being sufficiently large to allow water vapour or solvent to escape but sufficiently small to ensure that the material is kept within the container and wherein the material has been dried *in situ*.

Drying of the material may be carried out by any suitable drying process, for example, by freeze-drying or solvent evaporation. A review of the lyophilisation of pharmaceuticals is described for example by Williams and Polli in the Journal of Parenteral Science and Technology

(1984) Vol. 38 No. 2 p48 -50. A modified freeze-drying technique which may be employed is that disclosed in US5,648,093, wherein after freezing, the frozen water in the material is exchanged with a lower melting point solvent, such as ethanol and the ethanol is then removed by a drying technique. The above described freeze-drying process as applied to the present process may be more applicable since there is less exposure and handling of the material.

A further drying process that may be used is solvent evaporation. Many materials suitable for use in the present invention are prepared in non-aqueous solvents which are then subsequently evaporated away, leaving the material behind in the container.

If the preparation of a particular dried material dictates, the present method may be carried out under sterile conditions. Alternatively, the dried material in the container may be sterilised by suitable techniques such as dry heat sterilisation or UV or gamma irradiation.

Advantageously, the material to be dried is a drug formulation. The drug formulation comprises an active agent and an excipient. The excipient may be any one or a combination of a range of excipients typically used in drying applications, such as sugars, substituted celluloses biopolymers including gelatin and the like. The excipient may have a beneficial effect on the stability of the active agent. The excipient may include a polymeric gel forming component. The active agent may be dispersed homogenously

through the excipient, or may be localised within certain defined structures dispersed within the formulation, for example, within microspheres or other microenvironments.

The use of a polymer gel formulation as an excipient may facilitate active agent uptake and activity. Dried polymer gel formulations may hydrate to form bioadhesive gels. These gels have prolonged retention characteristics enabling them to remain in contact with absorbing mucosal surfaces for prolonged periods of time. This is particularly the case when the active agent is localised within the bioadhesive microenvironments of the excipient. The prolonged retention characteristics may improve the efficiency of the absorption process thereby improving the efficacy of the drug. The active agent(s) present in drug formulations may be absorbed through any absorbing mucosal, or similar, surface. Suitable surfaces are present in oral, nasal, rectal and vaginal mucosae, on the surface of the eye and on open wounds. Accordingly, the container of the present invention may be used to administer drugs via any of the aforementioned absorbing surfaces.

Thus the present invention also provides use of a container as described herein in the preparation of a dried medicament.

In a further aspect there is provided a dried pharmaceutical or pharmacological formulation prepared using the method as described herein.

A particularly preferred dried formulation may be obtained by drying a solution comprising mannitol, carboxypolymethylene, hydroxy propyl methyl cellulose or mixtures thereof and a pharmaceutical or pharmacological agent by, for example, freeze-drying. Such a formulation is particularly suited for preparation as a nasal insert or "bougie". The nasal insert or "bougie" may suitably be used for local administration of the pharmaceutical or pharmacological agent ie. in the region of the nose, or systemic administration. The nasal insert or "bougie" may be used to locally administer pharmaceutical or pharmacological agents such as antibiotics, antibacterial agents, hormones, stimulants such as nicotine or cannabis, anti-inflammatories, decongestants and the like for either a local or systemic effect.

Typically, the excipient, for example mannitol, carboxypolymethylene hydroxy propyl methyl cellulose or mixtures thereof may be present in solution prior to drying at a concentration of between 0.2% and 30%, preferably between 0.25% and 10% more preferably between 0.5% and 4%. By appropriate control of the excipient content in the formulation it is possible to regulate release of the pharmaceutical or pharmacological agent from the dried formulation.

The principle advantage of the nasal insert according to the present invention is that it provides a more precise dosing of agent compared to conventional liquid or powder sprays or drops.

Furthermore, the nasal insert allows the administration of non-aqueous agents which are unstable in aqueous solution. This is achieved by, for example, solvent evaporation of the agent, which then is contacted with the membrane of the nasal passages, thus substantially reducing contact between the agent and any aqueous environments.

Embodiments of the present invention may be used to dry drug formulations in unit doses.

Embodiments of the present invention will now be described, by way of example, with reference to the following drawings and tables in which:

Figure 1 is a perspective view of a container in accordance with a first embodiment of the present invention;

Figure 2 is a perspective view of a container in accordance with a second embodiment of the present invention;

Figure 3 is a schematic view of the container of Figure 2 in use;

Figure 4 is a graph showing the effect of weight of K4MP lyophilisate (n=10) on hardness;

Figure 5 is a graph showing the effect of weight of lyophilisate (n=10) on springiness;

Figure 6 is a graph showing the effect of concentration of K4MP (n=10) on hardness;

Figure 7 is a graph showing the effect of applied force on adhesive force of K4MP lyophilisate (n=10),

contact time 1 minute, hydration volume of water 30 μl;

Figure 8 is a graph showing the effect of contact time on adhesive force of K4MP (1.5% w/w) lyophilisate (n=10), test force 10 g; hydration volume of water 30 μl, mean weight of the lyophilisats 5.25 mg;

Figure 9 shows a schematic representation of a diffusion chamber used in testing the lyophilisates prepared according to the present invention;

Figure 10 is a graph showing the release profile of nicotine hydrogen tartrate (calculated as nicotine base) from lyophilisate prepared from 0.25% - 3% w/w solution, of K4MP in PBS, pH 7.4 at 37°C (n=4);

Figure 11 is a graph showing the release profile of nicotine hydrogen tartrate (calculated as nicotine base) powder and lyophilisate of different molecular weight Methocel grade K (2% w/w solution) in PBS, pH7.4 at 37°C (n=3);

Figure 12 is a graph showing the release profile of chlorhexidine gluconate from a 0.5% HPMC nasal plug; and

Figure 13 is a graph showing the release profile of chlorhexidine gluconate from a 1% HPMC nasal plug.

Reference is first made to Figure 1 which depicts a container 10 for use in a drying process in accordance with a first embodiment of the present invention. The container 10 comprises a blister film 12 with a plurality of depressions 14. The blister film 12 is further provided with an impermeable membrane 16 which is in sealing engagement with the blister film 12. The membrane is

provided with a number of holes 18. The container 10 is overpackaged with an material impermeable to the membrane 16 (not shown).

In use, a solution of a drug formulation is introduced into the depressions 14 of the blister film 12. The impermeable membrane 16 is placed over the blister film and sealed thereon. Holes 18 of 550 microns in diameter are pierced through the membrane as shown in Figure 1. The container 10 is placed in, for example, a freeze-dryer and freeze dried. During the drying process, water vapour or solvent escapes through the holes 18 to leave a dried plug of material in the depression. The container 10 is then sealed to prevent re-entry of water vapour or solvent through the holes 18.

Thus packaged, the drug formulation may be stored ready for use. The use of the container 10 above in a method of drying may be suitable for drying drug formulations for oral or other routes of administration.

Reference is now made to Figure 2 which depicts a container 40 for use in a drying process in accordance with a second embodiment of the present invention. The container 40 is formed of an impermeable membrane 42 of a plastics material. The membrane 42 is formed as a tube which is sealed at both ends. The container 40 is provided with a number of holes 44 in its surface. The holes 44 are resealed with a stamp sized seal (not shown).

The use of the container 40 is now described with reference to Figure 3. A solution of a drug formulation is introduced into the container 40 which is initially, sealed only at one end. The container 40 is filled with the desired volume of solution and sealed at "A". The container 40 is then placed in, for example, a freeze dryer and freeze dried. Water vapour or solvent escapes through the holes 44 in the container 40 to leave a substantially cylindrical rod of the dried drug formulation. The container 40 is then resealed to prevent the re-entry of water or solvent through the holes 44.

The container 42 may be used to produce drug formulations in a form suitable for nasal administration.

Further aspects of the present invention will now be illustrated by way of example with reference to the following examples.

Example 1

The following experiment investigates the relationship between hole diameter and rate of water loss during the freeze-drying process.

Samples I to IV (see Table 1) are placed in a freeze-dryer and freeze-dried for 24 hours at a temperature of -55°C and a pressure of 0.08 mbar. Samples II to IV are sealed with an impermeable membrane. Holes of 300 and 550 microns are made in the impermeable membranes of Samples III an IV respectively.

The % weight loss endured by the samples are recorded in Table 1.

(N.B. The solutions used in Samples II and IV were more viscous than those of Samples I and III).

Table 1

Samples	Hole diameter (microns)	Solution type	Hole area (mm^2)	% weight loss (water) in 24 hrs
I	open container	10% mannitol	132.67	90.0
II	sealed container	1.5% carbopol, 1.5% methocel, & 5% mannitol	0	0
III	300	10% mannitol	0.071	71.00
IV	550	1.5% carbopol, 1.5% methocel, & 5% mannitol	0.238	90.00

Additionally the rate of weight loss during freeze drying of samples in open containers versus containers containing a single 600 μm hole was determined (see Table 2). It can be seen that the rate of weight loss between open containers and those with a single 600 μm hole is practically negligible.

Table 2 Compilation of % vapour rate loss and r squared values during freeze-drying

Sample ID	Open		1 hole (600μm)	
	Slope (% vapour rate loss per hr.)	r^2	Slope (% vapour rate loss per hr.)	r^2
1.5% w/w mannitol sol.	8.1295	0.9631	8.124	0.9915
10% w/w mannitol sol.	7.6185	0.9952	7.5295	0.9867
1.5% w/w K100LVP sol.	8.2193	0.9298	8.3528	0.9292
1.5% w/w K4MP sol.	7.9721	0.8689	8.2128	0.9692

Example 2

This experiment investigates the relationship between the rate of water loss and the number of holes present in the impermeable membrane.

2ml of a solution of 1.5% methocel F50 Prem LV (Dow Chemical Company, USA) and 1.5% Carbopol 943P (Goodrich) is placed in each of seven vials I to VII.

Vial I is left open. Each remaining vial is covered with a polyethylene membrane approximately 80 microns thick. The polyethylene membrane is held in place by a rubber plug which forms a sealing engagement with the vial mouth. Each plug has a hole bored through its middle leaving a portion of the polyethylene sheet exposed.

Holes are made in the exposed polyethylene membrane of certain vials by piercing a 460 micron needle therethrough. 5 holes are made in Vial II, 10 in Vial III, 15 in Vial IV, and 20 and 25 holes are made in Vials V and VI respectively.

The containers are then prefrozen in liquid nitrogen and freeze dried for 24 hours at -55°C and a pressure of 0.078 mbar. The results are tabulated in Table 3.

Table 3

Vial	Characteristics* (area, mm^2)	24 h weight loss (%)
I	open	92.0
II	5 (0.166)	92.5
III	10 (0.332)	93.0
IV	15 (0.498)	93.0
V	20 (0.664)	92.0
VI	25 (0.830)	92.0
VII	sealed	0.0

* no. Of 0.46 mm diameter holes formed in membrane indicated.

As can be seen from the results, no water is lost from the sample in Vial VII. This indicates that the water loss from samples II to VI occurred exclusively through the 460 micron holes. The results also suggest that freeze-drying occurs as efficiently through a pierced impermeable sheet as it does from an open vial. The number of holes in the impermeable sheet does not appear to have an appreciable effect on percentage weight loss.

Example 3

In this experiment, the feasibility of freeze-drying hydrophilic polymer solutions is investigated. The polymers listed in Table 4 are dissolved in a suitable amount of water for a necessary period of time. 1 ml of each solution formed is placed into a vial. The vials are pre-frozen and placed in a freeze-dryer.

The polymer gel solutions are freeze dried for 24 hours at -50°C and at 0.08 mbar pressure. Table 5 illustrates the percentage weight loss from each of the samples.

Table 4

Polymer	Source	Conc.	Code
Carbopol 940	BF Goodrich	15 mg/ml	A
Carbopol 941	BF Goodrich	15 mg/ml	B
Carbopol 943P	BF Goodrich	15 mg/ml	C
Carbopol 974P	BF Goodrich	15 mg/ml	D
Carbopol 954	BF Goodrich	15 mg/ml	E
Povidone (Plasdone K-29/32)	ISP	15 mg/ml	F
PEG 4000	BDH	15 mg/ml	G
PEG 1500	BDH	15 mg/ml	H
Na-CMC (Low viscosity)	BDH	15 mg/ml	I
HPMC (6cps)	Shinetsu Chem.com Tokyo	15 mg/ml	J
MC (2500cps, Celacol Gum)	Courtauds Ltd.	15 mg/ml	K
HPMC	Courtauds Ltd.	15 mg/ml	L

Table 5

Code	24 h weight loss (%)	Code	24 h weight loss (5)
A	98.5	G	98.5
B	98.3	H	97.7
C	98.0	I	98.5
D	98.5	J	98.6
E	98.0	K	98.0
F	97.6	L	98.0

Example 4

This experiment shows how the concentration of the polymer gel solution used affects the rate of freeze-drying.

The following polymer gel solutions are prepared using Carbopol 934 manufactured by BF Goodrich (Table 6). The solutions were pre-frozen in liquid nitrogen and freeze-dried (24 hours, -50°C and 0.08mbar). The percentage weight loss from each of the polymer gel solutions is shown in Table 6.

Table 6

Sample Code	Conc. (%)	24 h weight loss (%)
A	1	97.96
B	2	97.23
C	3	97.12
D	4	90.24
E	5	96

Example 5

This experiment shows the evaluation of the mechanical properties, hydration characteristics and adhesive ability of lyophilisates prepared according to the present invention.

The lyophilisate was prepared essentially by filling polypropylene microcentriguge tubes with a solution to be freeze-dried and then freeze dried as in Example 4.

I. Characterisation of mechanical properties of lyophilisate

Evaluation of the mechanical properties of the anhydrous lyophilisate was performed by using TA.XT2 (version 5.19R) Texture Analyser, load cell capacity 25 kg (Stable Micro System, Godalming, England) in TPA mode. In this mode the probe compresses the test material twice, in this case, to a depth of 10mm and at a rate of 1.0mm/sec, with a delay period of 5 second between the end of first and beginning of the second compression.

The mechanical properties of hardness, fracturability (brittleness), springiness, and resilience were determined using a Texture Profile Analysis program (Jones *et al.*, 1996 *J. App. Polymer Sci.* 61, p2229-2234). These parameters determine the handling characteristics and perhaps patient compliance during administration of the product. The increased hardness and decreased springiness & resilience with increasing concentration of individual formulation components is shown in Figures 4, 5 & 6.

II. Hydration characteristics of lyophilisate

This was done visually on a watch glass using 2% w/v mucin solution (Hog stomach, Fluka) at 25°C. The lyophilisate was dropped onto the mucin solution and the collapse time (time at which there was no visual evidence of unhydrated material) was recorded. The total amount of water needed to hydrate lyophilisate was also determined.

The collapse time of lyophilisates, weight ranging from 5-40mg was less than 15 seconds. Lower weight range lyophilisates were hydrated even faster, 8 sec.

The total amount of water needed to hydrate lyophilisate i.e. to just hydrate it completely, depending upon the lyophilisate weight (5-40mg) was 50 - 120 microlitre.

III. Measurement of adhesivity of hydrated lyophilisates

This was performed by using Texture Analyser in adhesive mode with a contact time of one minute. The lyophilisates were prepared from 1.5 & 2.5% w/w solution of Methocel (K4MP). A volume of water (enough to hydrate at least half of the lyophilisate) was pipetted onto the glass slide; the lyophilisate was stuck on to the cylindrical probe which was positioned in such a way that it hits the centre of the water droplet.

To investigate the effect of contact time on adhesivity, adhesive force was measured at a fixed test force for different contact times and to investigate the effect of applied force, adhesive force was measured at various applied forces.

In the range studied, adhesive force increased with applied force (see Figure 7). This is in accordance with the work of Tobyn *et al.*, 1994 *International Labmate* Vol XVII, Issue VI. A similar trend of increasing adhesive force with contact time was also observed (see Figure 8).

Example 6

This experiment shows the *in vitro* drug release profile of lyophilisates prepared according to the present invention.

The lyophilisates were prepared as in Example 5.

Nicotine hydrogen tartrate (NHT), manufactured by Sigma-chemical company (Lot 17H1206), was chosen as the model drug. The release profile of NHT (calculated as nicotine base) was studied in a diffusion chamber (100, see Figure 9), which, with a minimal dissolution volume on the donor side, mimics the hydration condition of the nasal mucosa. The donor compartment (101) contains air saturated with water and the receptor compartment (103) contains PBS, pH 7.4 at 37°C. The lyophilisate (105) was placed on filter paper (107) which was maintained just in contact with the liquid phase of the receptor compartment (104) which is constantly agitated by a magnetic stirrer (109) (Cornaz *et al.*, 1996 *Int. J. Of Pharm.* 129 p175-183). Samples of 0.5 ml were withdrawn at regular time intervals through port (111), replaced by fresh medium through port (113) and spectrophotometrically analysed at 260 nm (UNICAM UV4-100 UV/Visible Spectrometer) after appropriate dilution.

The solutions of NHT (equivalent to 4mg of nicotine base per unit dosage; 1mg nicotine base is equivalent to 2.85mg of NHT) were prepared in different concentrations of hydroxy propyl methyl celulose (Methocel grade K of different mol. wt. Viz., K4MP (4,000 mol. wt.), K15MP (15,000 Mol. wt.), K100MP (100,000 Mol. wt.) and K100LV (100 Mol. wt.), Dow Chemical Company, USA); lyophilisate from these solutions were also prepared by transferring a fixed volume of solution, that will deliver 4mgs of nicotine, into the cylindrical microfuge tubes. These filled microfuge tubes were prefreezed with liquid nitrogen and lyophilised for 24 hours at -55 degree celcius and 0.08mbar pressure.

For release studies of NHT from polymer solutions, 0.65ml of solution, which contain the equivalent of 4mgs of nicotine base, was placed on the filter membrane in the donor compartment and sampling and assay was performed as described above.

The release profile of NHT (calculated as nicotine base) from Methocel K4MP solutions of different concentration (0.25 - 3% w/w solutions), lyophilisate prepared from these solutions, and lyophilisate prepared using different molecular weight grate K Methocels (K4MP, K15MP, K100MP, and K100LV) was studied. As a control, nicotine release from NHT powder and NHT solution was also studied.

The release of nicotine was dependent on the concentration of polymer in the formulation whether this was a solution or lyophilisate. The release rate decreased with polymer concentration in the formulation (see Figure 10).

Nicotine release from solution was faster than from lyophilisate prepared from the same solution (K4MP) (results not shown). This could be due to the higher viscosity of the hydrated lyophilisate. The difference became more prominent at higher concentrations. Unexpectedly, nicotine release rates from lyophilisates (prepared from 1 & 2% w/w solutions) of different molecular weight grades of Methocel K did not vary with molecular weight (Figure 11).

Example 7 - Desmopressin 10mcg Nasal Plugs

Preparation - Method

Desmopressin nasal solution manufactured by Ferring was purchased, containing 250μg/ml of desmopressin acetate. Using a microsyringe a 10μg dose was measured into each of 20 microcentrifuge tubes by measuring 0.1ml of the desmopressin solution. The micro centrifuge tubes containing the 10μg desmopressin dose were then flash frozen using liquid nitrogen, and freeze dried for 24 hours. This produced a very small amount of visible white powder in the microcentrifuge tubes containing a 10μg dose of desmopressin.

Hydroxypropyl-methylcellulose (HPMC) solutions of 1% and 2% were prepared using K4MP Methocel powder. Mannitol powder (0.8g) was weighed and dissolved in approximately 30ml of distilled water. The HPMC powder was then added slowly to the solution, with constant stirring using a magnetic stirrer. To prepare a 1% HPMC solution 0.8g of HPMC was added, and to prepare a 2% HPMC solution 1.6g of HPMC was added. When all of the HPMC powder had been added to the

appropriate solutions, stirring was continued until the powder was entirely wetted and dissolved into the solution. Distilled water was then added to the solutions to a final weight of 80g, and the solution was stirred further to ensure uniformity. The solutions were stored overnight at a constant temperature of 4°C in order to ensure that they were fully hydrated and that all air bubbles had been removed.

The 10μg freeze dried dose of desmopressin contained in ten of the microcentrifuge tubes was reconstituted by adding 0.6ml the 1% HPMC solution to each tube, and the desmopressin dose in the other ten tubes was reconstituted by adding 0.6ml the 2% HPMC solution to each tube. The resulting solution in each tube was stirred carefully using a needle to ensure that the entire desmopressin dose had been dissolved, and that the dose had been distributed uniformly throughout the solution. The 20 tubes containing the 10μg dose of desmopressin in HPMC solution were flash frozen using liquid nitrogen, and then freeze dried for 24 hours. The resulting nasal plugs were then stored in an airtight container at 4°C to avoid rehydration of the polymer, or degradation of the desmopressin.

Results

A solution of 6μg/ml desmopressin was analysed using UV Spectrometry. The resulting analysis showed no useful peaks however. Therefore the dissolution of the nasal plugs was examined using a Dissolution Bath. The plugs were weighed before they were added to the dissolution bath with the intention of re-weighing them at different time points during

the experiment, however it proved to be impossible to remove the hydrated mass efficiently from the bath during the experiment, and so instead observations were recorded. The results obtained for the nasal plugs containing 1% HPMC showed that after three hours of stirring in water at 37°C, there was still a visible mass of rehydrated nasal plug remaining in each of the six dissolution baths. The observations made for the 2% HPMC plugs were that after 5½ hours there was still a visible mass of hydrated HPMC present in each of the six dissolution baths. The amount of the plug left varied according to whether or not the plug had adhered to a surface within the bath, or had remained as a free mass floating within the water.

Example 8 - Chlorhexidine Gluconate Nasal Plugs

Preparation

Chlorhexidine gluconate 20% solution manufactured by Sigma was used to prepare chlorhexidine gluconate nasal plugs. The nasal plugs were required to contain an anti-bacterial dose of chlorhexidine gluconate equivalent to 0.5mg of chlorhexidine hydrochloride. Calculated as chlorhexidine base this is equivalent to 0.7759mg of chlorhexidine gluconate. As the chlorhexidine gluconate was a 20% solution, this meant that 1ml of this solution would contain 0.2g of actual chlorhexidine gluconate.

Hydroxyproply-methylcellulose (HPMC) solution of 0.5% and 1% were prepared using K4MP Methocel powder. Mannitol powder (0.8g) was weighed and dissolved in approximately 30ml

of distilled water, along with 0.4ml of the 20% chlorhexidine gluconate solution, in order to prepare a 1mg/ml final solution. The HPMC powder was then added slowly to the solution, with constant stirring using a magnetic stirrer. To prepare a 0.5% HPMC solution 0.4g of HPMC was added, and to prepare a 1% HPMC solution 0.8g of HPMC was added. When all of the HPMC powder was added to the appropriate solutions, stirring was continued until the powder was entirely wetted and dissolved into the solution. Distilled water was then added to the solutions to a final weight of 80g, and the solution was stirred further to ensure uniformity. The solutions were stored overnight at a constant temperature of 4°C in order to ensure that they were fully hydrated and that all air bubbles had been removed.

The nasal plus were prepared by adding 0.7ml of the 0.5% or 1% solutions to microcentrifuge tubes. This meant that each of the tubes would contain a dose of 0.7mg of chlorhexidine gluconate, which was easier to measure accurately using a syringe than 0.7759ml. The tubes containing the chlorhexidine gluconate solutions were flash frozen using liquid nitrogen, and the freeze dried for 24 hours. The resulting nasal plugs were then stored in a dessicator in order to avoid rehydration of the polymer.

Results

The release of chlorhexidine gluconate from the plugs was studied using a dissolution cell containing 25.5ml of distilled water, with filter paper as a membrane. The cell was kept at a temperature of 37°C. At various time points,

0.5ml of the acceptor reservoir was extracted, and the volume removed was immediately replaced with an equal volume of distilled water. The extractions were then analysed using UV Spectrometry, and the chlorhexidine gluconate content of the extracts was calculated according to the results produced from a series of calibration solutions. The results produced are shown in Figures 12 and 13.

Various modifications may be made to the above embodiments without departing from the scope of the invention. For example, the drug formulation may be introduced in the container 10, 40 through the impermeable membrane 16, 42 using a syringe and a filling needle. The containers 10, 40 may also be used to prepare dried drug formulations suitable for buccal, rectal and vaginal administration, as well as administration across mucosal surfaces present in, for example, open wounds and damaged skin.

Claims

1. A method of drying a material comprising the steps of:

providing a container which comprises an impermeable membrane,

placing the material into said container,

closing the container, and

drying the material in the container, wherein the closed container has one or more holes pierced therethrough, and wherein said hole or holes is/are sufficiently large to allow water vapour or solvent to escape but sufficiently small to ensure that the material is kept within the container.

2. A method according to claim 1 wherein the material is dried by freeze-drying.

3. A method according to claim 1 wherein the material is dried by solvent evaporation.

4. A method according to any preceding claim wherein said one or more holes are pierced through the container prior to closing said container.

5. A method according to claims 1 - 3 wherein said one or more holes are pierced through the container after closing said container.

6. A method according to any preceding claim wherein the material placed into the container is over packed.

7. A method according to any preceding claim wherein the container is sealed to prevent water vapour or solvent from diffusing into the container through the holes once drying is completed.

8. A method according to claim 7 wherein each hole is resealed.

9. A method according to any preceding claim wherein the material to be dried is introduced into the container before holes are made in the container.

10. A method according to claim 9 wherein the material to be dried is injected into the container by means of a filling needle so that a hole is made in the container at the time of filling.

11. A method according to any preceding claim wherein material to be dried is a pharmacological agent.

12. A container comprising one or more holes pierced therethrough, the hole or holes being sufficiently large to allow water vapour or solvent to escape but sufficiently small to ensure that the material to be dried is kept within the container.

13. A container according to claim 12 wherein said container comprises a blister film having a plurality of regular spaced depressions and an impermeable membrane comprising a plurality of holes, wherein the membrane is placed over the blister film and sealed thereon and wherein the hole or holes in the impermeable membrane are positioned over said depressions.

14. A container according to claim 13 wherein the impermeable membrane is placed over the blister film before the material to be dried is introduced into the blister film.

15. A container according to claim 14 wherein the material is introduced into the blister film through a hole in the impermeable membrane or by at least one filling needle which makes at least one hole in the membrane.

16. A container according to claim 13 wherein the impermeable membrane is placed over the blister film after the material to be dried is introduced into the blister film.

17. A container according to claims 12 - 16 wherein the membrane is formed of a plastics material or a laminate.

18. A container according to claims 12 - 17 wherein the blister film is in the form of a tray comprising a plurality of preformed semi-cylindrical cavities.

19. A container according to claim 12 wherein the container is composed entirely of an impermeable membrane in the form of a tube sealed at both ends.

20. A container according to claim 12 wherein the container is in the form of a sealed bag or pouch.

21. A container according to claim 12 - 20 wherein the holes in the impermeable membrane have a diameter in the range of 10 microns to 2 mm.

22. A container according to claim 21 wherein the holes in the impermeable membrane have a diameter in the range of 100 - 1000 microns.

23. A container according to claim 22 wherein the holes in the impermeable membrane have a diameter of 550 microns.

24. A container according to claims 12 to 23 wherein said container comprises the dried material therein.

25. A pharmacological formulation prepared by the method according to claim 1.

26. A pharmacological formulation according to claim 25 wherein said formulation is prepared as a nasal insert or "bougie".

27. A pharmacological formulation according to claims 25 and 26 wherein the pharmacological agent is selected from the group comprising antibiotics, antibacterial agents, hormones, stimulants, anti-inflammatories and decongestants.

28. A pharmacological formulation according to claim 27 wherein the pharmacological agents are selected from the group comprising nicotine, desmopressin and chlorhexidine gluconate.

29. A pharmacological formulation according to claims 25 - 28 wherein said pharmacological agent have either a local or a systemic effect.

30. A container for use in the method of drying according to any one of claims 1 - 11, wherein said container comprises one or more holes pierced therethrough, the hole or holes being sufficiently large to allow water vapour or solvent to escape but sufficiently small to ensure that the material to be dried is kept within the container.

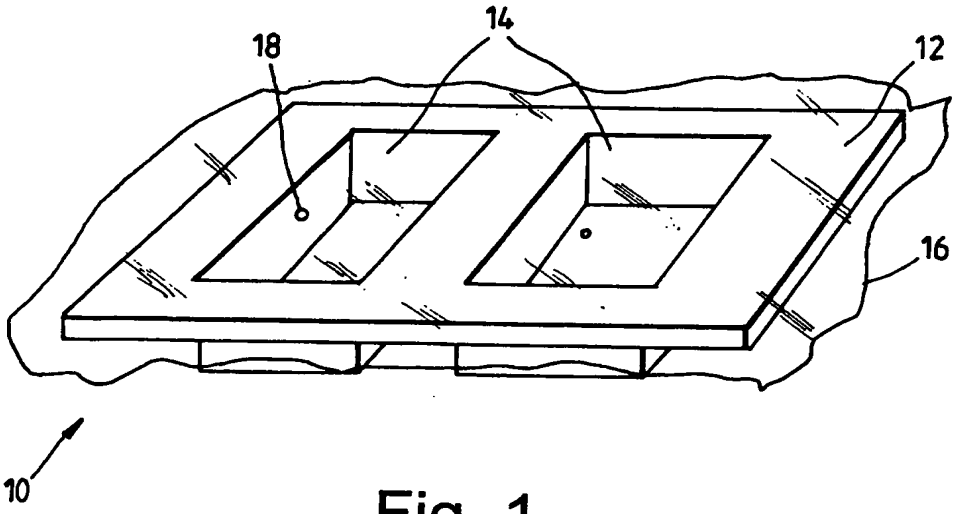

Fig. 1

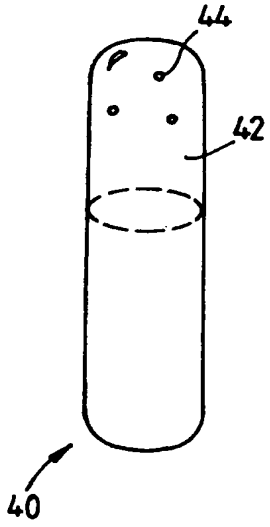

Fig. 2

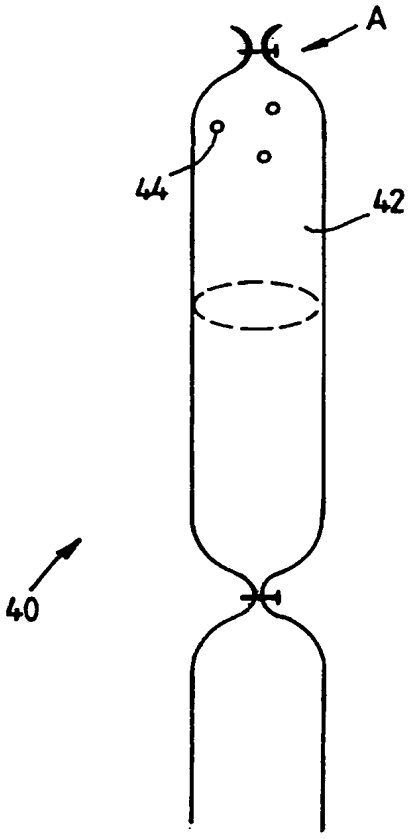

Fig. 3

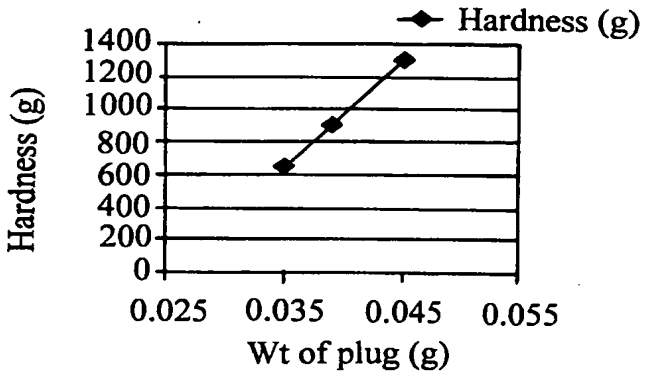

Fig. 4

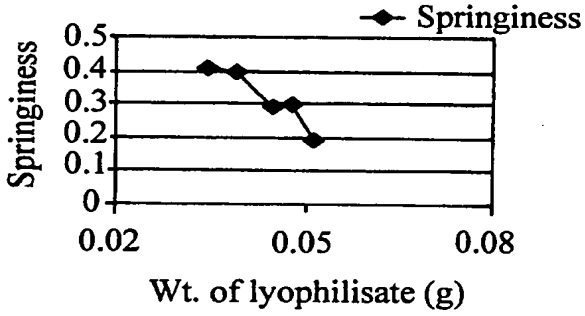

Fig. 5

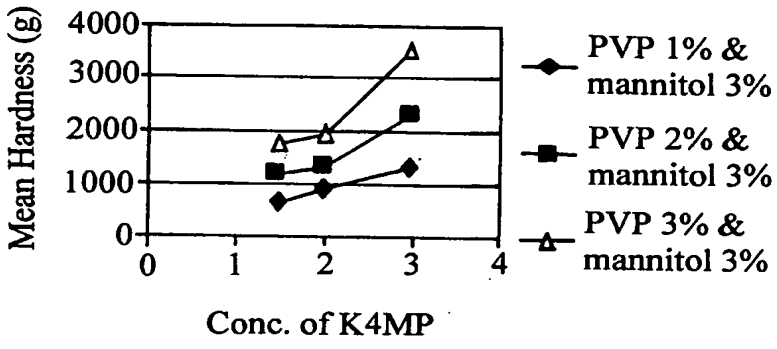

Fig. 6

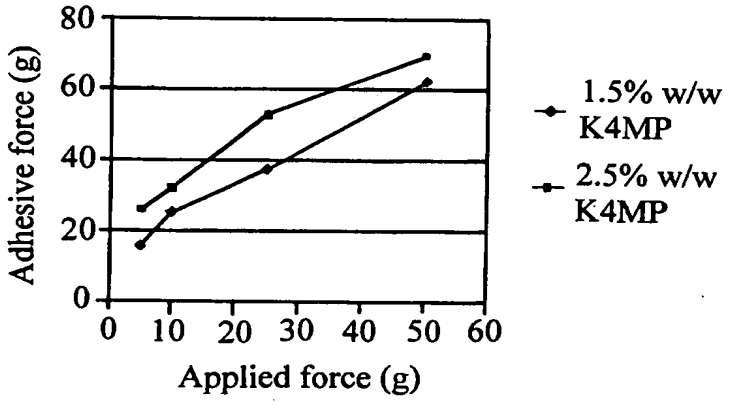

Fig. 7

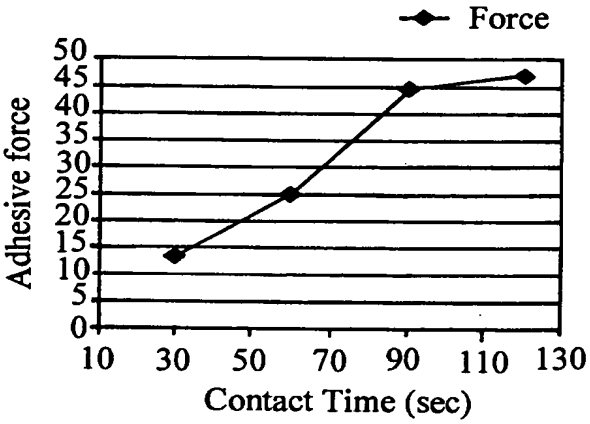

Fig. 8

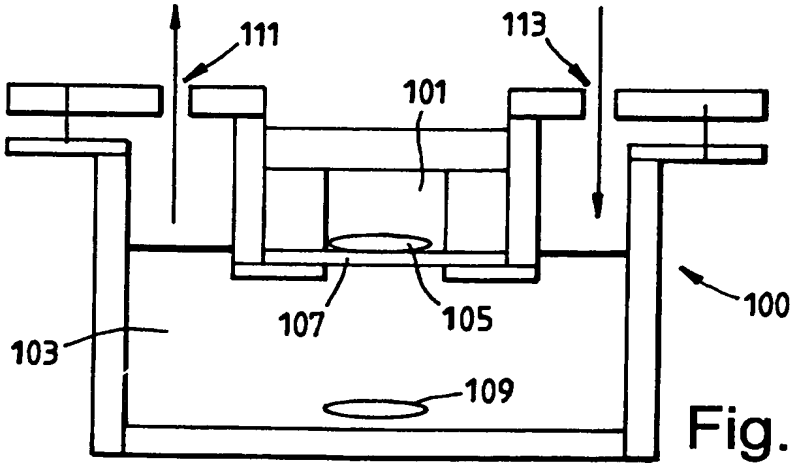

Fig. 9

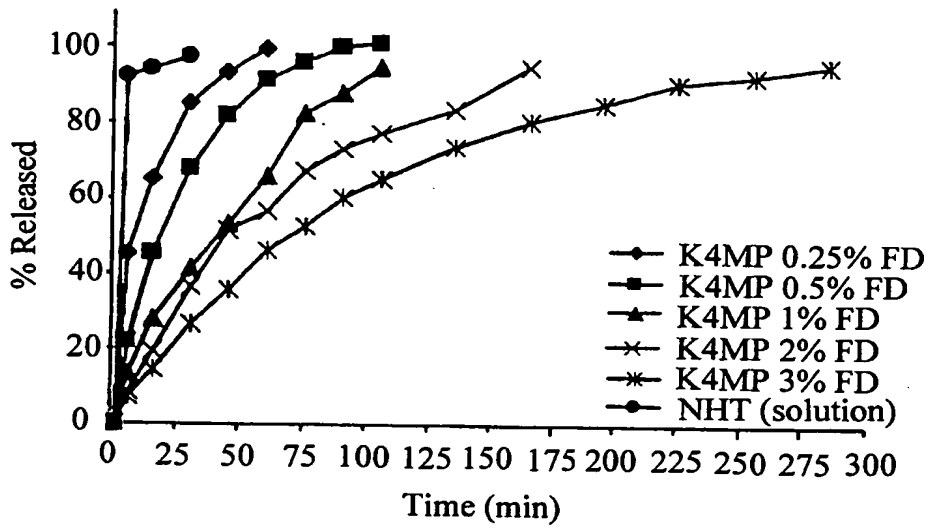
% Released
100
80
60
40
20
0
0 25 50 75 100 125 150 175 200 225 250 275 300
Time (min)
K4MP 0.25% FD
K4MP 0.5% FD
K4MP 1% FD
K4MP 2% FD
K4MP 3% FD
NHT (solution)

Fig. 10

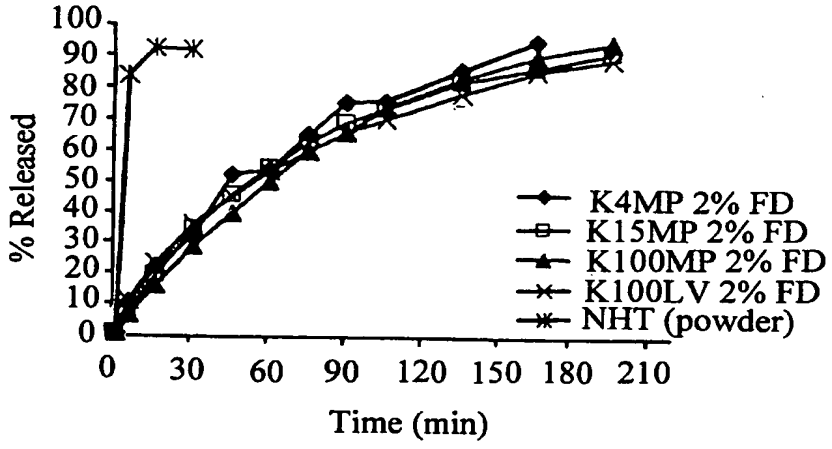
% Released
100
90
80
70
60
50
40
30
20
10
0
0 30 60 90 120 150 180 210
Time (min)
K4MP 2% FD
K15MP 2% FD
K100MP 2% FD
K100LV 2% FD
NHT (powder)

Fig. 11

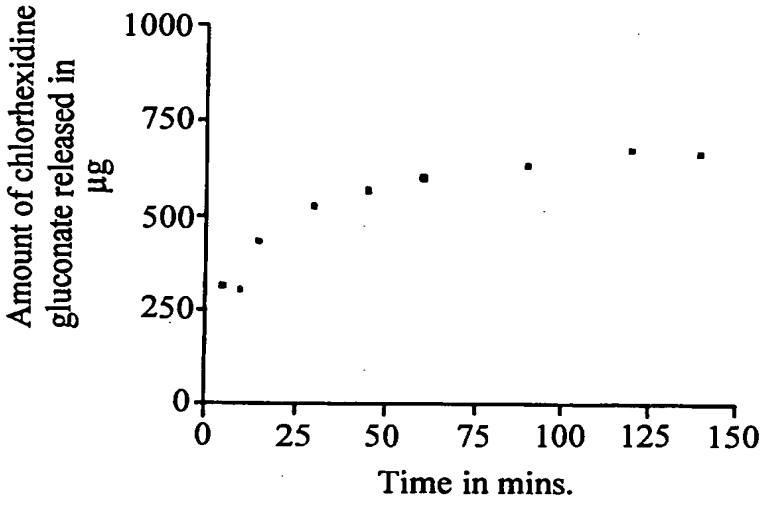
Amount of chlorhexidine gluconate released in µg
1000
750
500
250
0
0
25
50
75
100
125
150
Time in mins.

Fig. 12

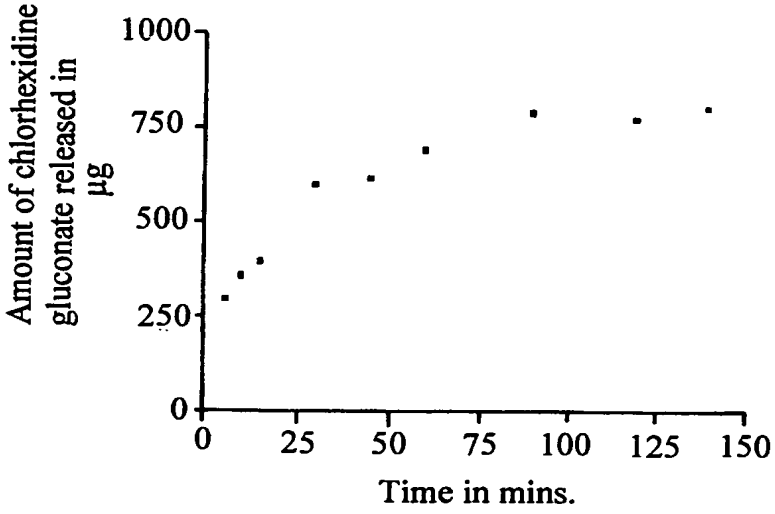
Amount of chlorhexidine gluconate released in µg
1000
750
500
250
0
0
25
50
75
100
125
150
Time in mins.

Fig. 13

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 99/04214

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 F26B5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 F26B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 97 11155 A (US HEALTH) 27 March 1997 (1997-03-27) page 8, line 26 -page 9, line 10 page 11, line 27 - line 33; figures 1-3	12,21, 22,24,30 1,2,7,9, 11
Y A	WO 96 31748 A (GORE & ASS) 10 October 1996 (1996-10-10) the whole document	1,2,7,9, 11 19,20
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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2000	31/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3018	Silvis, H

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 99/04214

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 309 649 A (BERGMANN THOMAS ET AL) 10 May 1994 (1994-05-10)	
A	WO 95 27180 A (GORE & ASS) 12 October 1995 (1995-10-12)	
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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